Clinical Study Report

TRALA

A Phase I Study of Targeted Radiotherapy alone for Stem Cell Transplant Conditioning in Systemic AL Amyloidosis

Short Title: ***T*argeted *R*adiotherapy for *AL*-*A*myloidosis – 'TRALA'.**

IMP: Yttrium-90 Radiolabelled Anti-CD66
Indication Studied: Systemic AL-Amyloidosis
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Note: **This Clinical Study Report contains confidential information.**

Short Title: *T*argeted *R*adiotherapy for *AL-A*myloidosis – 'TRALA'.

Study outline:

This was an open label, multi centre, phase I study. Three treatment levels with step-wise increase of the infused ^{90}Y-labelled anti-CD66 (^{90}Y-anti-CD66) radiation activity. The study recruited patients with Systemic AL-amyloidosis (S-ALA) due to undergo autologous stem cell transplantation. Patients require autologous peripheral blood stem cells to be collected and harvested by standard procedures and cryopreserved, sufficient for two transplant procedures prior to study consent as one of the eligibility criteria. The radiolabelled anti-CD66 was given fourteen days prior to the reinfusion of autologous stem cells.

Abstract

This trial was based on the results from phase I and II trials using the same IMP given as part of standard conditioning therapy prior to haematopoietic stem cell transplantation (HSCT) in patients with a wide range of haematological malignancies. A total of 85 patients undergoing either autologous or allogeneic stem cell transplantation have received the ^{90}Y-anti-CD66. The details of all trials and adverse events are detailed in the Investigators Brochure (IB). No serious adverse events causally associated with the radiolabelled antibody were seen and the estimated radiation dose delivered to the bone marrow showed a linear relationship to the administered dose. In a Phase I/II study, at the highest infused activity level, an estimated median of 36 Gray (Gy) of radiation was delivered to the bone marrow with 6.7Gy to the liver. In a Phase II randomised trial in patients with multiple myeloma, patients were randomised to receive either standard conditioning with high dose melphalan (HDM) or HDM plus the ^{90}Y-anti-CD66 at an infused activity of 37.5MBq/kg body weight. No additional toxicities were associated with the addition of the ^{90}Y-anti-CD66 to transplant conditioning and there was a statistically significant improvement in the number of patients achieving complete disease responses (CR) post transplantation in the investigational arm.

The rationale behind this study was that the ^{90}Y-anti-CD66 alone may have minimal toxicity and could potentially induce disease responses in patients with S-ALA, a patient group particularly vulnerable to toxicities from standard chemotherapy.

Study objectives:

Primary: Safety and toxicity of using ^{90}Y-anti-CD66 as the sole conditioning prior to autologous stem cell transplantation for AL-amyloidosis.

Measure: Specific organ toxicity as defined in CTCAE ver4.0. Overall number of Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions determined as causally related to the radiolabelled anti-CD66.

Secondary:

1. To determine the clonal response using the ^{90}Y-anti-CD66 mAb as targeted radiotherapy as measured by serial FLC assay. Responses will be summarised as recommended in the Consensus Guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis.

Measure: Disease response as determined by changes in the free light chain assay (FLCa) pre and post ^{90}Y-anti-CD66 and post transplantation (centralised laboratory, NAC).

2. To determine clonal response to the ^{90}Y-anti-CD66 mAb by following the change in malignant plasma cell population in bone marrow using established, validated methods of FLOW cytometry (Leeds HMDS).

Measure: Clonal plasma cell population as determined by FLOW cytometry pre and Day +100 post transplantation.

3. To determine disease response and cardiac recovery by measuring NT-proBNP levels pre and post (D100) therapy (centralised laboratory, NAC).

Measure: NT-proBNP levels pre and post (D100) therapy

4. To assess impact of using ^{90}Y-anti-CD66 mAb on time to progression and overall survival.

Measure: Assessment of TTP and OS.

5. To determine the utility of the dosimetry model developed in previous Phase I and II trials, using the same radiolabelled anti-CD66 and with imaging/dosimetry post ^{90}Y-anti-CD66.

Measure: Comparison of organ dosimetry from previous trials using the same antibody vector.

6. To determine the engraftment of autologous stem cells as determined by time to platelet recovery >20 and >50 x 10^9/L and neutrophils >0.5 x 10^9/L (EBMT criteria).

Measure: Tabulation of platelet and neutrophil engraftment

7. To assess the proportion of patients that form human anti-murine antibodies (HAMA) following exposure to anti-CD66 mAb in the context of an autologous stem cell transplant for AL amyloidosis.

Measure: HAMA assay results from samples taken at a defined interval post transplantation.

Summary of results by end-point outcome

Primary end-point

The study achieved the primary end-point by determining the toxicities associated with the use of the IMP as the only conditioning agent prior to ASCT in patients with S-ALA. A total of 47 Adverse Events (AEs) were recorded, the majority (41) were grades 1 or 2, 3 were grade 3 and 3 grade 4. None were reported as being life-threatening and no Serious Adverse Events (SAEs) and no Serious Unexpected Adverse Reactions (SUSARS) were recorded. A summary of recorded AEs is given in table 1 (page 20) and the full list in appendix 1. There were no transplant related deaths and all patients remain alive at the time of last follow-up.

Secondary end-points

All secondary end-points were achieved.

1. Disease responses were reported as determined by changes in clonal FLCa. Reductions in FLCa were documented in 7 of 9 patients who received the ^{90}Y-anti-CD66 and ASCT with 2 complete remissions (CR), 5 partial responses (PR), one stable disease (SD) and one progressive disease (PD) by D+100 post transplant. An additional patient achieved CR by FLC criteria after D+100 with a total of 3CRs at final data lock.
2. Disease responses were reported as determined by reduction in the percentage of clonal plasma cells in the bone marrow post ^{90}Y-anti-CD66 therapy and ASCT. Of eight patients that could be evaluated, 6 had a fall in the percentage of clonal plasma cells post ^{90}Y-anti-CD66 and ASCT. One patient was excluded from analysis as their BM samples were sent to a local laboratory rather than the central laboratory.
3. No consistent change in the level of NT-proBNP was recorded pre and post therapy, however there were no cardiac AEs recorded.
4. The trial follow-up period was limited to Day +100 post ASCT in that period one patient had disease progression (1 of 9 = 11.1%). Overall survival (OS) was 100% at Day +100. Further follow-up beyond Day +100 will be made by the National Amyloidosis Centre and these results may be added at a later date.
5. The dosimetry model developed in patients with haematological malignancies such as myeloma, acute myeloid and lymphoid leukaemia and chronic myeloid leukaemia was fully applicable to this patient group with biodistribution and organ dosimetry consistent with previous patients (dosimetry detailed in table 2).
6. All patients engrafted with no primary or secondary graft failures. Engraftment times were the same as seen in patient receiving standard chemotherapy conditioning prior to ASCT such as HDM (table 7).
7. Of the 9 patients that received the ^{111}In-anti-CD66 and the ^{90}Y-anti-CD66, 6 developed Human Anti Murine antibodies (HAMA) by D+100 post-transplant. These had no clinical significance.

Overview:

The study completed recruitment for the Phase I stage and did not expand any of the ^{90}Y-anti-CD66 activity levels. After the completion of each activity level cohort a report was prepared for review by the Independent Data and Safety monitoring committee (IDMC) detailing the results. A final report with all results was prepared at the end of the recruitment and follow-up period for the last patient entered. This was formally approved by the IDMC and a copy held by the Sponsor.

Trial management:

The trial was managed by an independent Clinical Research Organisation (CRO), Pharmexcel.

Trial Approvals

Ethics Committee

This study was reviewed by the South Central - Hampshire B Research Ethics Committee and approved on 13th November 2015. All amendments to the study have been submitted and approved where appropriate by the REC.

This study was conducted in accordance with the Declaration of Helsinki.

Regulatory Authority

This study was reviewed by the Medicines and Healthcare Regulatory Authority and approved on the 16th November 2015. All amendments to the study have been submitted and approved where appropriate by the MHRA.

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List of Abbreviations

AE	Adverse event
ALK PHOS	Alkaline phosphatase
ALL	Acute lymphoid leukaemia
ALT	alanine aminotransferase
AML	Acute myeloid leukaemia
APBSCT	Autologous Peripheral Blood Stem Cell Transplant
AST	aspartate aminotransferase
bd	Twice Daily
BGP	Biliary glycoprotein
BJP	Bence Jones Protein
BMT	Bone Marrow Transplant
BP	Blood Pressure
Bq	Becquerel
BSA	Body Surface Area
CEA	Carcinoembryonic antigen
cGy	centiGray
Ci	Curie
CPM	Clinical Project Manager
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCT	Direct Coomb's test
DFS	Disease Free Survival
DLT	Dose Limiting Toxicity
DMEC	Data Monitoring & Ethics Committee
DOTMP	1,4,7,10-tetraazcyclododecane-1,4,7,10-tetramethylenephosphonate
DTPA	Diethylenetriaminepentaacetic acid
ITC-DTPA	Iso-thiocyanato-DTPA
ECG	electro-cardiogram
EBMT	European Blood and Marrow Transplantation Organisation
EDTA	ethylene diamine tetra-acetic acid
EDTMP	Ethylene diaminetetramethylene phosphonate
FACS	Fluorescence Activated Cell Sorting
GIT	Gastrointestinal
GGT	Gamma glutamyltransferase
GMP	Good Manufacturing Practice
Gy	Gray
HAMA	Human anti-murine antibody
Hb	Haemoglobin
^{166}Ho	Holmium-166
HSCT	Haematopoietic Stem Cell Transplantation
^{131}I	Iodine-131
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
Ig	Immunoglobulin
^{111}In	Indium-111
ISF	Investigator Site File
Kg	Kilogram
LDH	Lactate dehydrogenase
LLR	Leukaemia and Lymphoma Research
LVEF	Left Ventricular Ejection Fraction
m^2	Metre squared

MAb	Monoclonal antibody
MBq	Mega Becquerel
mCi	milliCurie
MDS	Myelodysplastic syndrome
MeV	Mega electron volt
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Multi- Research Ethics Committee
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NR	No Response
od	Once Daily
OS	Overall survival
PD	Progressive Disease
PEFR	Peak expiratory flow rate
PI	Principal Investigator
Plts	Platelets
PK	Pharmacokinetics
PR	Partial Response / Partial Remission
QC	Quality control
RBC	Red Blood Cells
RECs	Research Ethics Committees
^{188}Re	Rhenium-188
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SD	Stable Disease
SDS	Sodium dodecyl sulphate
SOP	Standard Operating Procedure
^{153}Sm	Samarium-153
SPECT	Single photon emission tomography
$T_{½}$	Terminal elimination half-life
T4	Thyroxine
TBI	Total body irradiation
tds	Three Times Daily
TMG	Trial Management Group
TRM	Transplant related mortality
TSC	Trial Steering Committee
TSH	Thyroid stimulating hormone
UHS	University Hospital Southampton NHS Foundation Trust
vgPR	Very good Partial Remission
WBC	White Blood Cells
WHO	World Health Organisation
^{90}Y	Yttrium-90

Plain English Summary

Systemic AL-amylodosis (S-ALA) is a serious haematological condition related to multiple myeloma and is characterised by the deposition of AL-amyloid protein fibrils in various organs such as the heart, liver, spleen and kidneys causing severe impairment of function. The amyloidogenic protein is produced by clonal plasma cells that are present in the bone marrow. Patients with S-ALA can respond to similar treatment strategies used to treat myeloma including high dose chemotherapy and autologous stem cell transplantation which can result in control of the disease and improvement in survival, however S-ALA patients are more difficult to treat as they frequently have additional medical problems such as impaired kidney and cardiac function which can result in significant toxicities associated with high dose therapy. This limits the number of patients that can receive high dose therapy but even with careful patient selection and screening the morbidity and mortality associated with autologous stem cell transplantation is much higher than for patients with myeloma.

The Targeted Radiotherapy Group in Southampton developed a technique of preparing patients for transplantation using a radiolabelled monoclonal antibody that targets the bone marrow allowing very precise delivery of high radiation doses to the site of disease, in this case the clonal plasma cells. The TRALA trial was a Phase I study designed to find the optimal radiation dose that can be delivered safely to patients and to determine if this was associated with a reduction in the production of amyloidogenic protein. The study was conducted at five sites in the UK, University Hospital Southampton NHS FT (UHS), Royal Free Hospital NHS FT (RFH), University College Hospital NHS FT London, Royal Victoria Infirmary, Newcastle Hospitals NHS FT and Queen Elizabeth University Hosiptal Birmingham NHS FT. The Southampton group provided essential technical support with treatment delivered in UHS and the RFH. Patients returned to their home centre for autologous transplantation after the targeted radiotherapy had been given. The trial was based on several years of pre-clinical and clinical research using the radiolabelled monoclonal antibody in patients undergoing autologous or allogeneic stem cell transplantation for haematological malignancies. The group have previously shown that very high doses of radiation can be safely delivered to the bone marrow with minimal radiation to other organs. In theory, if radiation could be directed specifically to sites of disease in patients with S-ALA (bone marrow and spleen) then the benefits of radiation could be used but avoiding the unwanted toxicity to normal organs. This is the basic concept behind targeted radiotherapy.

Scientific summary

S-ALA is classified as a clonal plasma cell disorder, the clonal free light chains produced by the plasma cells form complexes that accumulate in tissues eventually leading to organ dysfunction and ultimately failure. The aim of treatment is to reduce or eradicate the clonal plasma cell population, eliminating production of the clonal FLC and allowing time for tissue repair to remove the FLC complexes from tissues with improvement in function. Treatment usually involves the use of agents that are used to treat the related condition multiple myeloma. Unlike myeloma, the total clonal plasma cell population is usually small, it is the consequence of FLC complexes accumulating in tissues that causes harm. Autologous stem cell transplantation (ASCT) has been shown to improve disease responses and hence survival in patients with S-ALA but the treatment is poorly tolerated due to disease-related co-morbidities with a high transplant related morbidity and mortality (1).

The hypothesis of this study was that targeting radiation to sites of disease by using a monoclonal antibody that targets normal bone marrow cells may result in an improvement in the response rate post-transplant but without increasing toxicity to non-haematopoietic organs. The selected target antigen, CD66, is expressed on normal myeloid tissue and has been shown to be present on normal and malignant plasma cells (2, 3). As such CD66 is an ideal target for molecular radiotherapy (MRT). The choice of radionuclide for attachment to the anti-CD66 monoclonal antibody must take into consideration several factors such as availability, ease of radiolabelling, gamma radiation emission to permit individual patient imaging and dosimetry and beta particle emission to deliver the therapeutic radiation. No single radionuclide has the ideal combination of characteristics. For this study the isotope indium-111 was selected for imaging and dosimetry while the high-energy beta emitting isotope yttrium-90 was chosen for therapy. Both are classified as radiometals and require the use of a metal-chelating molecule for stable attachment to protein. In this study we have used a derivative of DTPA, CHX-A”-DTPA, as the chelating agent. The chelation of the monoclonal antibody and

radiolabelling procedures were based on well-established technologies with modifications as required for full GMP manufacture and for ICH-GCP clinical trial regulations.

Background

Prognosis and therapy of S-ALA:

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited as abnormal, insoluble fibrils that progressively disrupt tissue structure and impair function. S-ALA, which is the commonest amyloid type, occurs in a small proportion of individuals with monoclonal B cell dyscrasias (4). AL fibrils are derived from monoclonal immunoglobulin light chains, which are unique in each patient underlying the remarkably heterogeneous clinical picture in this particular form of amyloidosis; virtually any organ or combination of organs other than the brain may be affected. S-ALA has a lifetime incidence and is the cause of death of between 0.5-1 per thousand individuals in the UK. It occurs equally in men and women and the median age at diagnosis is 65 years. Without therapy it is inexorably progressive and until recently the median survival was just 6-15 months (5). Patients with S-ALA receive treatment with the same agents that are used to treat multiple myeloma, although the use of some drugs is limited by toxicity in S-ALA patients. Autologous stem cell transplantation (ASCT) has also been used, first reported in 1996, and a series of 25 patients was reported by Comenzo and colleagues (6, 7). Several centres subsequently reported clinical benefit in about 60% of patients who survived the procedure. However, treatment-related mortality was substantially and consistently higher among patients with amyloid than those with myeloma. The 100-day mortality in two experienced single-centre US studies was around 14% and in two multi-centre European studies was ~40%, reflecting compromised function of multiple organ systems by amyloid (8). These findings highlighted the need for refinement in patient selection for ASCT and improvement in peri-transplant clinical management whilst also prompting interest in alternative, less toxic, therapeutic regimens.

Chemotherapy and Autologous Stem Cell Transplantation for AL amyloidosis

After the immunoglobulin nature of AL amyloidosis was established case reports claiming beneficial responses to cytotoxic therapy appeared in the literature. Efficacy of oral melphalan and prednisolone (MP) was systematically compared to colchicine, effectively a placebo, in a prospective randomised trial of 219 patients by the Mayo Clinic group. Median survival were 17 months and 8.5 months in the MP and colchicine groups respectively, demonstrating robustly for the first time the benefit of cytotoxic therapy in AL amyloidosis (9). In an attempt to identify which patients with AL amyloidosis were likely to derive the greatest benefit from therapy with MP, the Mayo Clinic investigators reported long term follow-up of 153 patients who received this therapy for a planned 24-36 months (10). Using stringent response criteria which included complete disappearance of any pre-treatment serum or urine monoclonal protein in conjunction with improvement in organ dysfunction, 18% of patients responded. The median survival among responders was 89.4 months and the median time to achieve a response was 11.7 months. However, one-quarter of responders died of myelodysplasia or acute leukaemia.

The relatively poor and delayed responses to MP in AL amyloidosis prompted interest in use of high dose melphalan therapy and stem cell transplantation (ASCT). This was first reported in 1996, and a series of 25 patients was reported shortly afterwards by Comenzo and colleagues (6). Several centres subsequently reported clinical benefit in about 60% of patients who survived the procedure. However, treatment-related mortality was substantially and consistently higher among patients with amyloid than those with myeloma. The 100-day mortality in two experienced single-centre US studies was around 14% and in two multi-centre European studies was ~40%, reflecting compromised function of multiple organ systems by amyloid (8). These findings highlighted the need for refinement in patient selection for ASCT and improvement in peri-transplant clinical management whilst also prompting interest in alternative, less toxic, therapeutic regimens.

In the US, patient selection was refined (8) and ASCT has remained the therapeutic “gold-standard” in AL-amyloidosis. Results of long-term follow-up of 701 consecutive patients with systemic AL-amyloidosis were recently reported by the Boston Group; 394 (56%) were considered eligible for ASCT of whom 82 did not proceed because of patient choice or disease progression (11). Treatment Related Mortality (TRM) among 312 patients who initiated therapy was 13%

and median survival for the whole cohort was 4.6 years. Median survival among ineligible patients was only 4 months. Interestingly, Dispenzieri *et al* examined data from patients with AL-amyloid treated at the Mayo clinic from 1983 to 1997 and identified 229 patients who would now have been eligible for ASCT. Their median survival was 42 months and 5 and 10 year survival rates were 36% and 15% respectively, suggesting that the survival benefit with ASCT is, in part, due to patient selection rather than the specific therapeutic regimen (12). A French randomized trial cast further doubt on the role of ASCT in AL amyloidosis due to high treatment related mortality of ~22% and no improvement in overall survival in the ASCT arm over oral melphalan dexamethasone chemotherapy in a landmark analysis (13). However, the high TRM and lower than expected responses has led to much criticism of this study. The role of ASCT therefore remains unclear and practice in the UK National Amyloidosis Centre has recently been to rarely recommend ASCT as first line therapy but to consider its role in patients who have not responded adequately to first line therapy. Outcome among all 92 patients with AL amyloidosis who were seen at the UK National Amyloidosis Centre and underwent ASCT between 1994 and 2004 was recently determined, the median overall survival for the whole cohort was 63 months and although TRM was 23%, retrospective analysis identified a subset of patients with no TRM (14). Factors identified from the NAC study lead to refinement of patient selection criteria in the UK and data from 2003-2011 from 83 patients undergoing ASCT revealed a TRM of 6%.

Even in a highly selected patient group, TRM and morbidity of the treatment persists. Majority of the treatment morbidity is due to the toxicity of high dose melphalan leading to mucositis, end organ damage due to the drug or complication of cytopenias. Within this study, we would therefore expect a TRM of <5% in patients fulfilling the eligibility criteria for the high intensity pathway especially as targeted radiotherapy is not expected to cause significant end organ damage. It is anticipated that toxicity would be much lower than with a high dose melphalan ASCT. In a Phase I study in patients undergoing ASCT for multiple myeloma using a ^{90}Y-anti-CD66 together with high dose melphalan (200mg/m^2) the TRM was zero (n = 16), five of these patients had received the same infused activity of ^{90}Y-anti-CD66 (37.5MBq/kg lean body weight). In a subsequent Phase II trial the TRM remains zero (n = 12) at the same activity level of ^{90}Y-anti-CD66. A summary of the clinical experience to date with the ^{90}Y-anti-CD66 in the context of HSCT is provided in the attached Investigator's Brochure (IB). As a safety factor the first infused radiation activity level will be below that established as the MTD in the Phase I trial, the first activity level will be 30MBq/kg lean body weight.

Disease response in AL-amyloidosis as measured by changes in the FLCa has been shown to have important prognostic significance. In a large retrospective analysis of 816 patients treated in seven large amyloid centres in Europe and the USA using variety a of treatments including autoSCT (16%) there was a strong correlation between the extent of reduction of the amyloidogenic free light chain and improvement in survival. Response as determined by fall in FLCa at 3 months post initiation of treatment (15). There was a highly significant improvement in survival for patients that had achieved a CR compared with those that had achieved a PR or less. In addition, a marker of cardiac function NT-proBNP, also shows a correlation with degree of fall in FLCa post therapy, indicating a probable causal relationship between the level of persisting FLC and cardiac recovery or continued damage. The NT-proBNP levels have been proposed as a biomarker of disease response in patients with AL-amyloidosis (15, 16).

Targeted Radiotherapy

Targeted radiotherapy, selectively delivering therapeutic doses of radiation by intravenous infusion, is a logical development for the treatment of multiple myeloma, having the potential to deliver additional therapy without increasing toxicity to non-target organs. In addition the continuous, low dose rate delivered by the natural decay of a targeted radionuclide may have a greater destructive effect upon tumour cells than single dose or fractionated external beam radiation (17, 18). Radiation may be directed to sites of disease by two methods. Indirectly, by the use of bone seeking agents such as bisphosphonates or directly by attaching a radionuclide to a vector that can target bone marrow cellular components and/or malignant plasma cells. For the indirect targeting of disease two agents have been used clinically in patients with multiple myeloma; 1,4,7,10-tetraazcyclododecane-1,4,7,10-tetramethylenephosphonate (DOTMP) radiolabelled with the radionuclide holmium-166 (^{166}Ho-DOTMP) (19) and ethylenediaminetetramethylene phosphonic acid (EDTMP) radiolabelled with Samarium-153 (^{153}Sm-EDTMP) (20). In a phase I trial of ^{166}Ho-DOTMP used with high dose melphalan and APBSCT, a high incidence of renal and bladder toxicity

was recorded. This was due to the rapid excretion of the radiolabelled DOTMP and the relatively short half-life of ^{166}Ho, requiring bladder irrigation. Marked variation in the radiation dose delivered to red marrow was also a problem (21). Less toxicity was seen with ^{153}Sm-EDTMP, however radiation dose delivered to the limb skeleton was low.
Targeted radiotherapy, using a monoclonal antibody as vector targeting haematopoietic tissues, could allow treatment intensification without toxicity to non-haematological tissues and may improve dose distribution to red marrow.

Targeted therapy for haematological malignancies

The feasibility of using targeted radiotherapy for the treatment of haematological malignancies and as part of preparative regimens prior to stem cell transplantation has been explored by several groups using both animal models and in clinical trials with encouraging results (22-29) reviewed in (30-32)(33). There are two components required for targeted radiotherapy, a vector, such as a monoclonal antibody, which determines specificity and secondly a radionuclide. Targeting is achieved by selecting a vector that specifically interacts with an antigen present on tumour cells. The radiolabelled antibody is usually administered intravenously. Accumulation of antibody and thus radionuclide within the tumour allows imaging, from which dosimetry can be estimated, and subsequent therapy. For the treatment of haematological malignancies, antigens used as targets in clinical trials include CD33, CD45, CD66, CD20 and CD19. None of the above antigens are specifically expressed by malignant cells derived from haematological tissue, all are present on the normal cell counterpart from which the malignant cell is derived. In practice, when using targeted radiotherapy in the context of stem cell transplantation, it is the bone marrow that is targeted. Malignant cells such as leukaemic blasts or myeloma cells diffusely infiltrate normal haematopoietic cells, indeed the majority of patients undergo stem cell transplantation when in remission with minimal tumour burden. Thus, radiation delivered by a monoclonal antibody vector specific for an antigen present on haematopoietic tissue will destroy normal and tumour cells indiscriminately causing grade IV myelotoxicity. However, in the context of stem cell transplantation, this is acceptable. Of greater importance is the ability for targeted radiotherapy to deliver significant levels of radiation to the bone marrow (and spleen) without toxicity to non-haematopoietic tissues (34).

Matthews *et al* reported the results of a phase I study using an anti-CD45 murine monoclonal antibody radiolabelled with iodine-131 ([^{131}I]) combined with standard chemotherapy and TBI as the conditioning therapy prior to bone marrow transplantation for patients with poor risk AML, ALL and transformed myelodysplasia (25)(35). The targeted therapy was well tolerated and estimated absorbed doses of radiation to the bone marrow was 2-4 fold that of the dose to non-haematological tissues. Toxicity to non-haematopoietic organs was not in excess of that associated with standard conditioning regimens. 10 of 34 (30%) patients remained in complete remission (median 65 months). This study was primarily designed to determine the maximum tolerated dose of radiation that could be delivered. However, for a comparable patient group with poor risk leukaemia the disease free survival in published series is in the order of 25% (36). In a phase II study, anti-CD45 targeted radiotherapy combined with busulphan and cyclophosphamide without TBI has been used as a conditioning regimen prior to allogeneic BMT for patients with standard risk acute leukaemia. 18 of 24 patients transplanted remained in complete remission (75%) with a median time from transplant of 18 months, there were 2 relapses and 2 non-relapse deaths (infection and graft versus host disease). Scheinberg (Memorial Sloane Kettering) has used a ^{131}I-radiolabelled anti-CD33 monoclonal antibody in a phase I radiation dose escalation trial treating patients with relapsed or refractory myeloid leukaemia. Gamma-camera imaging demonstrated localisation of radiolabelled antibody to the bone marrow in 22 of 24 patients treated and reduction of circulating and bone marrow blasts in the majority of patients. In eight patients treated at the higher doses of ^{131}I, disease reduction was sufficient to allow subsequent allogeneic bone marrow transplantation with 3 patients achieving a remission. The maximum tolerated dose of radiation was not reached. The same group is now exploring the use of radiolabelled anti-CD33 as part of BMT conditioning; preliminary clinical results have been reported. As previously, no additional toxicity has occurred. Results derived from dosimetry indicated that the minimum myeloablative dose of radiation delivered to the bone marrow was in the order of 0.3 mCi (approximately 12 MBq) per kg body weight (37).

These phase I trials demonstrate that, by selecting an appropriate target antigen, haematopoietic cells can be selectively targeted and radiation delivered to sites of disease involvement with minimal toxicity to non-

haematopoietic tissues. Responses were obtained in patient's refractory to standard chemotherapy and there appears to be a decrease in the relapse rate for the patients in the Seattle studies.

Hepatic uptake has been apparent using antibodies with specificity for haematopoietic antigens (38)(39) and has limited the dose of radiation that can be used for therapy. However, Seitz *et al* reported the organ dosimetry of a rhenium-188 (^{188}Re) labelled anti-CD66 monoclonal antibody that has been available for several years as an *in vivo* white cell imaging agent, (Anti-granulocyte BW250/183). Excellent bone marrow targeting was achieved with considerably less liver uptake than reported for other antibody vectors (40). Bunjes *et al* have reported the results of incorporating the same anti-CD66 antibody in transplant conditioning when radiolabelled with ^{188}Re for patients with poor-risk AML or transformed MDS (29). Of 36 patients undergoing stem cell transplantation, the disease-free survival at 18 months was 45%; patients in remission at the time of transplantation achieved a CR rate of 67% compared to 31% in those not in remission. Orchard et al have reported excellent bone marrow targeting with the anti-CD66 murine monoclonal antibody BW250/183 (INN Besilesomab) radiolabelled with ^{111}In for imaging and dosimetry then ^{90}Y-labelled for therapy. Uptake by non-haematopoietic organs such as the liver and kidneys was low (41).

Selection of indium-111 (for imaging) and yttrium-90 (for therapy)

Yttrium-90 (^{90}Y) has been used for targeted immunotherapy by a number of groups treating a wide range of malignancies and has specific characteristics that make it suitable for the treatment of haematological malignancies. It has a relatively short physical half-life (2.7 days) allowing therapy and transplantation in a practical time-frame. The decay product is a high energy beta-particle (2.27 MeV maximum, 0.931 MeV average) delivering a high dose-rate with a maximum tissue penetration of 11mm, mean range 4mm. These figures are for a 'standard' tissue, which are considered to be predominantly water. However the penetration of beta-particles in bone marrow consisting of cellular marrow spaces and mineralised bone trabeculae is not known but is likely to be reduced. The lack of any gamma-radiation substantially reduces the radiation exposure of adjacent non-haematopoietic tissues. Radiation exposure to staff during the preparation of antibody immunoconjugate and during the care of the patient is negligible. In the phase I study, less than 5% per day of the injected dose of ^{90}Y is excreted in urine. These characteristics have allowed patients to be treated in part as outpatients in Phase I and II trials. The lack of gamma-radiation makes any preliminary dosimetry with ^{90}Y difficult, however Indium-111 (^{111}In) has been shown to effectively substitute for ^{90}Y and allow accurate prediction of tissue radiation exposure with ^{90}Y (42). ^{111}In has a half-life of 2.8 days, emitting gamma-radiation with energy between 0.17-0.24 MeV suitable for external imaging.

Selection of yttrium-90 dose levels for therapy

In the phase I study patients received a maximum ^{90}Y infused activity of 37.5 MBq per kg lean body weight. The Maximum Tolerated Dose (MTD) in the phase I study was defined as the dose level at which 2 or more patients at any dose level experienced a dose limiting toxicity related to the antibody and/or radiation therapy. The most significant toxicities were haematopoietic, but this was predictable and acceptable in the context of stem cell transplantation. The next most significant organ toxicity was gastrointestinal (GIT) with nausea, vomiting, oral mucositis and diarrhoea. However, grade 3 and in some patients grade 4 GIT toxicities are seen following high dose melphalan alone. No significant nausea and vomiting were seen in patients following ^{90}Y-anti-CD66 antibody, nausea and vomiting often occurred after melphalan in all radiation dose levels. There was a trend for more severe oral mucositis at the highest dose level but still within acceptable limits for transplantation. Further radiation dose escalation may be possible in the context of autologous transplantation but only if the dose of melphalan is reduced. In the conditioning prior to allogeneic SCT the same ^{90}Y-anti-CD66 has been used with a lower dose of melphalan (140mg/m^2), in this context a higher infused activity level of 45MBq/kg body weight has been well tolerated. No systematic study of a 'safe' bone marrow dose delivered by targeted radiotherapy has been published, however in the report by Matthews et al (25) graft failure was seen in a single patient that had received 31Gy to the bone marrow in addition to 12Gy as total body irradiation, a total of 43Gy to the bone marrow. The authors concluded that there was a possibility that the stromal environment had been damaged resulting in a failure of engraftment.

Although the administered dose of ^{90}Y (in MBq) will be primarily set by the lean body weight, as an additional safety measure, the radiation dose received by the liver and bone marrow as determined from dosimetry calculations will have upper limits. These were: ***For the liver a maximum dose of 15Gy***

For the bone marrow a maximum dose of 45Gy

If the dosimetry calculation (using data from ^{111}I] gamma imaging) indicated in any individual patient that the predicted liver dose will exceed 15Gy or the bone marrow dose exceeded 45Gy the dose of administered ^{90}Y radioactivity was proportionally reduced to achieve the maximum permitted dose ceiling(s).

The phase I trial results indicate that 45MBq/kg lean body weight is well tolerated when used in conjunction with 140mg/m^2 of melphalan. The toxicity profile for patients with S-ALA receiving high dose chemotherapy is more exaggerated than in patients with myeloma, consequently, although no melphalan will be used in the preparative schedule, the starting level for ^{90}Y-anti-CD66 will be 30MBq/kg, the second treatment level 40MBq/kg and the third 45MBq/kg.

TRIAL MEDICATION

For the purpose of this protocol, the IMPs for the trial are:

CHX A"-DTPA anti-CD66 antibody (Drug Substance)
^{111}In- CHX A"-DTPA anti-CD66 antibody (Drug Product A)
^{90}Y- CHX A"-DTPA anti-CD66 antibody (Drug Product B)

These are detailed in the Investigational Medicinal Product Dossier (IMPD).

Study objectives:

Primary: Safety and toxicity of using ^{90}Y-anti-CD66 as the sole conditioning prior to autologous stem cell transplantation for AL-amyloidosis.

Measure: Specific organ toxicity as defined in CTCAE ver 4.0. Overall number of Serious Adverse Events, Serious Unexpected Adverse Events determined as causally related to the radiolabelled anti-CD66.

Secondary:

1. To determine the clonal response using the ^{90}Y-radiolabelled anti-CD66 mAb as targeted radiotherapy as measured by serial FLC assay. Responses will be summarised as recommended in the Consensus Guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis.

Measure: Disease response as determined by changes in the free light chain assay (FLCa) pre and post ^{90}Y-labelled anti-CD66 and post transplantation (centralised laboratory, NAC).

2. To determine clonal response to the ^{90}Y-radiolabelled anti-CD66 mAb by following the change in malignant plasma cell population in bone marrow using established, validated methods of FLOW cytometry (Leeds HMDS).

Measure: Clonal plasma cell population as determined by FLOW cytometry pre and Day +100 post transplantation.

3. To determine disease response and cardiac recovery by measuring NT-proBNP levels pre and post (D100) therapy (centralised laboratory, NAC).

Measure: NT-proBNP levels pre and post (D100) therapy

4. To assess impact of using ^{90}Y-labelled anti-CD66 mAb on time to progression and overall survival.

Measure: Assessment of TTP and OS.

5. To determine the utility of the dosimetry model developed in previous Phase I and II trials, using the same radiolabelled anti-CD66 and with imaging/dosimetry post ^{90}Y-labelled anti-CD66.

Measure: Comparison of organ dosimetry from previous trials using the same antibody vector.

6. To determine the engraftment of autologous stem cells as determined by time to platelet recovery >50 x 10^9/L and neutrophils >0.5 x 10^9/L (EBMT criteria).

Measure: Tabulation of platelet and neutrophil engraftment

7. To assess the proportion of patients that form human anti-murine antibodies (HAMA) following exposure to anti-CD66 mAb in the context of an autologous stem cell transplant for AL amyloidosis.
Measure: HAMA assay results from samples taken at defined intervals post transplantation.

Assessment and management of risk

This was a study of targeted radiotherapy for stem cell transplant conditioning in S-ALA. There was no administration of standard high dose chemotherapy for such patients. Most risk and toxicity during an autologous stem cell transplant in S-ALA is due to the systemic toxicity of the high dose chemotherapy. Since there was no systemic high dose chemotherapy, the risks during the autologous stem cell transplant were predicted to be significantly lower than standard clinical care. Patients were selected to meet criteria for ASCT as per the standard clinical criteria and hence be a relatively fit group of patients. The teams in Southampton and the Royal Free are experienced in use of targeted radiotherapy in treatment of haematological malignancies. Trials with the same antibody in transplant conditioning for multiple myeloma and for allogeneic stem cell transplantation had been run in these sites previously and the radio-pharmacies and the radiation physics teams are experienced in use of the modality of treatment. No toxicities directly attributable to the use of the radiolabelled anti-CD66 have been seen in any of the trials to date. Summaries of the clinical experience with the IMP in the context of autologous and allogeneic stem cell transplantation can be found in the current versions of the Investigators Brochure (IB) and IMPD. We anticipate no increase in risk and likely a much lower risk to the patient in this study than standard high dose melphalan-ASCT for patients with AL amyloidosis.
This trial was therefore categorised as: Type A = No higher than the risk of standard medical care

Methods

Eligible patients were recruited in clinic by their treating haematologist. Potential study candidates were given the Patient Information Sheet (PIS) and allowed a minimum of 24 hrs to read the PIS and to discuss with family and friends. At a subsequent visit the patient had the opportunity to discuss the study with the clinical research team. After giving informed consent a schedule of trial and transplant events was prepared and shared with the teams responsible for both research related events and standard of care; the schedule was also given to the patient. The General Practitioner was informed of the involvement of the patient in the study if the patient permitted. Patients received an infusion of the ^{111}In-anti-CD66 in the department of Nuclear medicine in either UHS or RFH with gamma camera imaging as detailed in the protocol using whole body planar and SPECT-CT imaging on days 1 (day of infusion), 2, 4 and 5. Dosimetry was performed using the scanned images and the estimated absorbed radiation dose to specific organs calculated using the dosimetry model developed in Southampton. If the dosimetry showed more than two-fold radiation dose to the BM compared to the liver dose the patient proceeded to receive the infusion of ^{90}Y-anti-CD66, again in the respective department of Nuclear Medicine under supervision. the activity determined from cohort and patient lean body weight (using the Boer formula available from https://www.calculator.net/lean-body-mass-calculator.html). All samples of blood and bone marrow were taken either within study requirements or as standard of care. Patients were reviewed 7 days after infusion and study samples taken and then admitted to the appropriate transplant unit when becoming neutropenic, this occurred 9 – 11 days post ^{90}Y-anti-CD66. Autologous stem cells were infused 14 days after ^{90}Y-anti-CD66 in all patients without any additional chemotherapy of radiotherapy conditioning. While in hospital patients had daily medical reviews and results recorded in study Clinical Record Forms (CRF). Any adverse events were recorded with grading (using CTCAE version 4.0), causality and date of onset and resolution recorded. All events were reviewed by the local Principle Investigator as required by Good Clinical Practice (GCP) regulations. Patients remained in hospital until neutrophil engraftment (neutrophils >0.5 x 10^9/L) and independent of platelet support (platelets >20 x 10^9/L). Further reviews were as for local standard of care except for day 30 and 100 post-transplant which were required for the study.

Screening and Consent

Consent for the trial was taken after a successful stem cell harvest, at the local transplant centres by designated staff on the delegation log. Dated entries relating to the informed consent process must be made in the patient's medical notes. The patients will be provided with a screening number (S01, S02 etc). The original signed consent form was filed at each site in the site file, a copy filed in the medical notes and a copy given to the patient.
The patient's GP will be informed of their participation with the consent of the patient.

The participant remained free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment was provided with a contact point where he/she could obtain further information about the trial. If occurring, patient withdrawal of consent from the trial was explicitly documented in the source documents.

TRIAL DESIGN

This was an open label, Phase I multi-centre study, assessing the use of a radiolabelled anti-CD66 in patients with AL-amyloidosis with regard to:

Safety and Toxicity

Disease response. Progression from one dose level to the next was dependent on the toxicity profile demonstrated but not based on disease response. Patients were recruited from those attending the National Amyloidosis Centre for diagnosis and monitoring of their disease and in whom high dose therapy would be a treatment option.
There were three treatment levels, representing increasing infused radiation activity levels:

1) 30.0 MBq/kg lean body weight [^{90}Y]-radio-labelled murine anti-CD66
2) 40.0 MBq/kg lean body weight [^{90}Y]-radio-labelled murine anti-CD66
3) 45.0 MBq/kg lean body weight [^{90}Y]-radio-labelled murine anti-CD66

Toxicity:

For Treatment levels 1 (30.0MBq/kg) and 2 (40.0MBq/kg) patients were recruited sequentially and received treatment according to the dose level active at that time. As a safety factor, a gap equivalent to D+30 post-transplant passed before the next patient was treated at the same dose level and D+60 post-transplant between dose level 1 and 2. No patients experienced toxicity >CTCAE grade 2 at treatment level 1 and treatment level 2 (as defined in section 8.9). After closure of Treatment level 2, the scheduled IDMC meeting reviewed the safety data to date approved an amendment to patient treatment for Treatment level 3.

Amendment - For treatment level 3 (45.0 MBq/kg), patients were recruited and treated concurrently. After a patient 1 had undergone dosimetry, the next patient 2 could be consented and commence screening activities. Once patient 1 has completed Dosimetry and is scheduled for Treatment (90Y), patient 2 could undergo Dosimetry. No two patients would proceed through Dosimetry at the same time period. This allowed Cohort 3 to be completed with the potential to expand this cohort.

Disease response:

Disease response (change in FLC) was determined for each patient over the study period. Because of the co-morbid conditions that can affect patients with S-ALA it was not appropriate to demonstrate a clear MTD (i.e. by further increases in the infused radiation activity) if good clinical disease responses are achieved as indicated by reduction in the FLCa and clonal plasma cell population post therapy and transplant. The optimal infused radiation would produce a CR rate in all patients without demonstrable toxicity. The results from this Phase I study will be used to inform the format of further trials (Phase II) which would be designed to determine the optimal infused radiation activity and hence estimated bone marrow radiation dose in this specific patient group. If no toxicity was demonstrated at any infused activity level expansion of the third level to 6 patients was permitted to help provide additional evidence for disease response.

STUDY SETTING

Patients were recruited across 5 participating centres:

Table 1: Participating centres

Site	Name	Principal Investigator
01	University Hospital Southampton NHS Foundation Trust	Dr Kim Orchard
02	The Royal Free London NHS Foundation Trust/	Dr Ashutosh Wechalekar
02a	University College Hospital NHS Foundation Trust	Dr Ashutosh Wechalekar
03	University Hospitals Birmingham NHS Foundation Trust- The Queen Elizabeth Hospital	Dr Mark Cook
04	The Newcastle upon Tyne Hospitals NHS Foundation Trust-Freeman Hospital	Professor Graham Jackson

All radiolabelling work was undertaken at Sites 01 (Southampton) and 02 (Royal Free Hospital). Patients returned to the transplant centres for their remaining treatment.

All patients were previously clinically assessed in the NAC as standard of care for AL-amyloidosis patients in the UK.

Participants

A final total of ten (10) patients were recruited out of a potential maximum of 12 planned (if any cohort had been expanded). All patients had confirmed S-ALA, were in PR were considered eligible for an ASCT procedure if using HDM.

ELIGIBILITY CRITERIA

All patients with systemic AL-amyloidosis who meet eligibility criteria for ASCT in amyloidosis and have an indication for autologous stem cell transplantation as the preferred treatment option were eligible for this study.

Inclusion criteria

Patients with the following characteristics were eligible for this study

- Aged ≥18 years.
- Have a diagnosis of systemic AL-amyloidosis, either as a new diagnosis or recurrent disease.
- Measurable clonal plasma cell dyscrasia (FLCa) [1].
- Amyloid related organ dysfunction or organ syndrome.
- Estimated life expectancy of at least 6 months (as defined at trial entry).
- Sufficient stem cells for two transplant procedures[2].
- Bone Marrow (BM) cellularity >20%.
- Eligible for ASCT in AL amyloidosis defined as fulfilling ***all*** of the following criteria[3]:
    - ECOG Performance Status of 0 or 1 (Appendix 1)
    - Cardiac troponin-T <0.07 µg/L
    - NYHA heart failure class of <3 (Appendix 1)
    - No more than 3 organs involved by amyloidosis by consensus guidelines.
    - Creatinine clearance or isotope GFR ≥30ml/min.
    - Bilirubin ≤1.5 times and alkaline phosphatase ≤3 x upper limit of normal.
    - AST or ALT <2.5 x upper limit of normal range.
    - Absence of clinically important amyloid-related autonomic neuropathy[4].
    - Absence of clinically important amyloid-related gastro-intestinal haemorrhage.

[1] The following test are performed as part of routine standard of care and NAC evaluation therefore the data obtained and used will be prior to consent for the trial.
[2] Patients with previous stem cell harvest will be considered.
[3] The following test are performed as part of routine standard of care and NAC evaluation therefore the data obtained and used will be prior to consent for the trial.
[4] Borderline cases please contact PI at Royal Free Hospital

- Capable of providing written, informed consent.
- Women of child bearing potential should use adequate forms of contraception.
    - Intrauterine Device (IUD)
    - Hormonal based contraception (pill, contraceptive injection etc.)
    - Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
    - True abstinence (this is defined as refraining from heterosexual intercourse after receiving ^{111}In at the Dosimetry and Imaging visit through to final study visit.

Exclusion criteria

Patients with the following characteristics were ineligible for this study (see list of abbreviations for definitions)

- Overt symptomatic multiple myeloma.
- Amyloidosis of unknown or non-AL type.
- Localised AL-amyloidosis (in which amyloid deposits are limited to a typical single organ, for example the bladder or larynx, in association with a clonal proliferative disorder within that organ).
- Trivial or incidental AL amyloid deposits in the absence of a significant amyloid-related organ syndrome (e.g., isolated carpal tunnel syndrome).
- NYHA Class III or IV heart failure.
- Liver involvement by amyloid causing bilirubin >1.5 times upper limit of normal.
- Concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other *in situ* carcinomas.
- Pregnant, lactating or unwilling to use adequate contraception as listed above.
- Intolerance / sensitivity to any of the study drugs.
- Positive Human anti-murine antibodies (HAMA).
- Unable to provide written informed consent
- Involved in another IMP trial

OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Primary objective

The main objective of the study was to determine the toxicity associated with the use of the ^{90}Y-labelled anti-CD66 as the sole conditioning prior to autologous stem cell transplant in patients with AL-amyloidosis. Toxicity determination will be measured by CTCAE version 4.0 criteria and stem cell engraftment and hence establish the maximum tolerated radiation dose (MTD) over three infused radiation activity levels.

Secondary objectives

In addition the study will allow the assessment of clonal response (as measured by serial FLC assay) and by using established, validated methods of FLOW cytometry to measure the change in malignant plasma cell population. Disease response, cardiac recovery, time to progression and overall survival will also be reviewed, whilst determining the engraftment status of patients.

Finally the study will allow the assessment of the dosimetry model previously developed in Phase I and II trials in this patient group.

Outcome measures/endpoints definitions

Primary outcomes

1. Toxicity of [^{90}Y]-labelled anti-CD66 monoclonal antibody as the sole conditioning regime for autologous stem cell transplantation in patients with systemic AL-amyloidosis using CTCAE criteria.

Secondary outcomes

1. To determine the clonal response using the ^{90}Y-radiolabelled anti-CD66 mAb as targeted radiotherapy as measured by serial FLC assay. Responses will be summarised as recommended in the Consensus Guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis (16).
2. To determine clonal response to the ^{90}Y-radiolabelled anti-CD66 mAb by following the change in malignant plasma cell population in bone marrow using established, validated methods of FLOW cytometry.
3. To determine disease response and cardiac recovery by measuring NT-proBNP levels pre and post (D100) therapy.
4. To assess impact of using ^{90}Y-labelled anti-CD66 mAb on time to progression and overall survival.
5. To determine the utility of the dosimetry model developed in previous Phase I and II trials using the same radiolabelled anti-CD66 and with imaging/dosimetry post ^{90}Y-labelled anti-CD66.
6. To determine the engraftment of autologous stem cells as determined by time to platelet recovery >50 x 10^9/L and neutrophils >0.5 x 10^9/L (EBMT criteria).
7. To assess the proportion of patients that form human anti-murine antibodies (HAMA) following exposure to anti-CD66 mAb in the context of an autologous stem cell transplantation for AL amyloidosis.

Primary endpoint/outcome

Primary outcome

Toxicity of ^{90}Y-anti-CD66 monoclonal antibody as the sole conditioning regime for autologous stem cell transplantation in patients with systemic AL-amyloidosis as determined from the incidence of AEs using CTCAE version 4.0 and reportable SAEs, SARs and SUSARs causally associated with the IMP.

End of trial

The end of trial was defined as the date of the last patient reaching day +100 post-transplant.

STATISTICS AND DATA ANALYSIS

The appointed trial statistician will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

Sample size calculation

This trial was designed to recruit a maximum of 12 patients if treatment level 3 is expanded. If no toxicities are seen at any level, the trial will complete recruitment without expansion of the final dose level enrolling a total of 9 patients.

Planned recruitment rate

The planned recruitment rate is 4-6 patients per year for 2 years.

Statistical analysis plan

As this is not a comparative trial, but a phase I dose finding study, no comparative analyses will be performed. The primary and secondary study end-points, as detailed above, and all toxicities are summarised and reported in tabular form, with narrative descriptions of the DLTs experienced. With only 3 patients per group, as a minimum, standard deviations and standard errors are not meaningful; consequently any analysis has concentrated upon reporting the data as collected. The same information will be provided to the Data Monitoring Committee for their interim meetings; summarising not only the data from the cohort under investigation, but also the cumulative experience within the trial so that a full picture of the trial can be obtained.

Recruitment

Patients details (no patient identifiable information). Patients were recruited between July 2016 – February 2020.

Cohort dose level 1 n = 3

CD66-01001

68yr female, lambda light chain AL-amyloidosis with renal involvement diagnosed April 2015. Nephrotic syndrome, renal impairment, CKD stage 2. No cardiac amyloid.

Treatment: Cyclophosphamide, thalidomide and dexamethasone May – October 2011, minimal response; velcade + dexamethasone Dec 2011 – April 2012, PR; Revlimid + dexamethasone Feb – June 2015, minimal response; cyclophosphamide, pomalidomide + dex December 2015. Poorly tolerant of treatment. ECOG 1, NYHA 3.

CD66-01002

55yr male, kappa light chain AL-amyloidosis diagnosed 2012. Nephrotic syndrome, CKD stage 1, hypertensive, renal impairment. SAP scan showed large hepatic, renal and splenic amyloid load.

Treatment: Cyclophosphamide, thalidomide + dexamethasone x6 cycles, achieved very good PR; progression 2014, received GSK anti-SAP antibody x2 doses. Clonal progression. ECOG 0, NYHA 2

CD66-01003

69yr male, lambda light chain AL-amyloidosis diagnosed July 2015. Nephrotic syndrome, renal impairment with CKD stage 1, in-dwelling defibrillator.

Treatment: Cyclophosphamide, velcade + dexamethasone x3 Aug – Sept 2015, no response; revlimid, cyclophosphamide + dexamethasone x 1 Jan 2016; disease progression July 2016. ECOG 1, NYHA 3

Cohort dose level 2 n = 4

CD66-02004

56yr old male, Systemic AL amyloidosis in December 2015 with stage I CKD and nephrotic range proteinuria. Renal involvement, no cardiac amyloid deposition. Renal biopsy confirmed amyloid of AL lambda type. IgG lambda secreting plasma cell dyscrasia with presenting lambda light chains of 228 mg/L and paraprotein of 6g/L.

Treatment: Cyclophosphamide-Bortezomib-dexamethasone (VCD) to a partial response. However, he remained symptomatic and there was a subtle increase in the light chains. A lambda monoclonal band persisted in urine immunofixation. ECOG 0 and NYHA 2.

CD66-03005

58yr male, IgM lambda paraprotein and lambda light-chains with amyloid deposition in gut presenting in 2014 with a history of gastro-intestinal bleeding at presentation. Possible mesenteric node involvement. Treatment: VCD x6 with partial response; bendamustine and dexamethasone with improved PR. Disease progression 2017 with rising IgM paraprotein and lambda FLC co-incident with symptoms of easy-filling during meals and weight loss. ECOG 0, NYHA 2.

CD66-01006

63yr male, lambda light-chain AL-amyloidosis diagnosed 2012. Soft tissue involvement with amyloid deposition in tongue, salivary glands but no visceral organs. Previous treatment CVD x6 cycles April – Sept 2012, stem cell harvest and autologous SCT November 2012. Progression 2015 and salvage with VRD Nov 2015 – April 2016. Further progression 2017 treated with lenalidomide and dexamethasone x18 months. Completed treatment July 2018 but rising FLC. ECOG 0, NYHA 2.

Entered study but failed dosimetry with high uptake in liver and did not receive infusion of yttrium-90 labelled anti-CD66. Left study.

CD66-01007

67yr male, lambda light-chain AL-amyloidosis diagnosed 2010. Cardiac, tongue involvement. Previous treatment CTD x6 cycles Sept 2010 – March 2011; stem cell harvest and ASCT Jan 2012 achieving CR; Progression Feb 2018 with rising lambda FLC, treated in anti-SAP antibody trial July 2018 but further progression with slowly rising FLC.

ECOG 0, NYHA 2.

Cohort dose level 3 n = 3

CD66-01008.

70yr female, lambda light chain AL-amyloidosis diagnosed 2009.

Nephrotic syndrome, renal impairment, CKD stage 3. No cardiac amyloid on SAP scan; small renal load.

Previous treatment:

CTD x3 June – Aug 2009; velcade + dexamethasone x6 Aug 2009 – Jan 2010; Melphalan 200mg/m^2 ASCT Feb 2010; progression 2018 and velcade, dex, thalidomide Oct 2018 – Feb 2019; progressive disease, switched to Ixazomib, dex + revlimid x3 cycles to PR. CABG 2008. ECOG at trial entry 1, NYHA 1.

CD66-01009

62yr female, lambda light chain AL-amyloidosis diagnosed November 2013.

Nephrotic syndrome, hypertensive, renal impairment.

Minimal cardiac amyloid on SAP scan, renal amyloid on biopsy.

Previous treatment: Cyclophosphamide, velcade + dexamethasone Sept – Dec 2013. Achieved CR. Progression Oct 2017, slowly rising FLC. ECOG at trial entry 0, NYHA 1.

CD66-01010

69yr male, lambda light chain AL-amyloidosis diagnosed September 2009.

Cardiac involvement, nephrotic syndrome, renal impairment.

Previous treatment: Cyclophosphamide, dexamethasone + thalidomide Sept 2009 – March 2010; melphalan 200mg/m^2 ASCT Jan 2012 achieved CR. Progression early 2018. Treated in GSK trial with anti-SAP antibody + CPHPC, discontinued due to large vessel vasculitis.

ECOG at trial entry 1, NYHA 1.

RESULTS

Primary end-point:

Safety and toxicity of using ^{90}Y-anti-CD66 as the sole conditioning prior to autologous stem cell transplantation for AL-amyloidosis.

Measure: Specific organ toxicity as defined in CTCAE ver 4.0. Overall number of Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions determined as causally related to the radiolabelled anti-CD66.

Table 2: Toxicities

Patient ID	Serious adverse events	SUSARS	Adverse events			TRM*	OS**
			Mild	Moderate	Severe		
CD66-01001	0	0	4	1	0	0	Alive
CD66-01002	0	0	2	0	0	0	Alive
CD66-01003	0	0	2	0	0	0	Alive
CD66-02004	0	0	6	0	1	0	Alive
CD66-03005	0	0	4	0	1	0	Alive
CD66-01006[#]	0	0	0	0	0	0	Alive
CD66-01007	0	0	4	0	0	0	Alive
CD66-01008	0	0	6	0	0	0	Alive
CD66-01009	0	0	11	2	1	0	Alive
CD66-01010	0	0	2	0	0	0	Alive

*Transplant related mortality at D+100 ** Patient status at time of report.

[#]Patient did not receive ^{90}Y-anti-CD66 and left the study after imaging and dosimetry

AE grading 'mild' = CTCAE grades 1; 'moderate' = CTCAE grade 2; 'severe' = CTCAE grades 3 or 4; 'serious' = SAE as per standard criteria.

Total number of AEs 47; Mild = 41; moderate = 3; severe = 3.

Details of AEs recorded: Summarised in table 1. Data return 100%.

Summary:

No SAEs or SUSARs were experienced by patients in any dose cohort. All patients experienced profound cytopenias with neutropenia, thrombocytopenia and anaemia, entirely consistent with suppression of bone marrow function following targeted radiotherapy. These were not recorded as AEs as allowed in the study protocol, only non-haematological AEs were reported or any AEs that were a consequence of a cytopenia, for example neutropenic fever, haemorrhage.

Adverse events were mainly minimal grade 1-2 only. No AEs were causally related to the IMP. Two episodes of fevers during the neutropenic phases in two patients but although recorded as 'severe' due to the CTCAE grading system, as the patients were neutropenic at the time of fever, the patients were not clinically unwell and responded to antibiotic treatment. One patient (CD66-03005) experienced a gastrointestinal bleed during the period of thrombocytopenia. This patient had a previous history of GI bleeding prior to trial entry. No mucositis was experienced in any patient and all patients maintained oral nutrition. One patient had diarrhoea with stool positive for *C. difficile*. The majority of the AEs were related to pre-existing comorbid problems associated with AL-amyloidosis. No Dose Limiting Toxicity (DLT) was seen.

Details of all AEs are given in Appendix 1.

Secondary End-points:

1. To determine the clonal response using the ^{90}Y-anti-CD66 mAb as targeted radiotherapy as measured by serial FLC assay. Responses will be summarised as recommended in the Consensus Guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis.

Measure: Disease response as determined by changes in the free light chain assay (FLCa) pre and post [^{90}Y]-labelled anti-CD66 and post transplantation.

Sample time points:

1. Screening; day of ^{90}Y-anti-CD66 therapy (= D 0)
2. 7 & 14 days after ^{90}Y-anti-CD66 therapy
3. Day +30 and +100 post-transplant
   Total number of samples = 6

Table 3: FLCa results

Cohort 1

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01001	SCREENING PACK	08-Jul-16		12.3	82.2	0.15
CD66-01001	VISIT 2 PACK ^{90}Y TREATMENT	03-Aug-16	0	8.6	65.8	0.13
CD66-01001	VISIT 2 EXTENSION DAILY PACK	10-Aug-16	7	8.4	49.8	0.17
CD66-01001	VISIT 3 EXTENSION POST TRANSPLANT	17-Aug-16	14	7.5	12.7	0.59
CD66-01001	VISIT 4 FOLLOW UP DAY 30	19-Sep-16	+33	7	22.6	0.31
CD66-01001	VISIT 5 FOLLOW UP DAY 100	28-Nov-16	+103	7.7	25.9	0.3

Response = CR

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01002	SCREENING PACK	24-Aug-16		65.8	33.6	1.96
CD66-01002	VISIT 2 PACK ^{90}Y TREATMENT	21-Sep-16	0	95.8	40	2.4
CD66-01002	VISIT 4 FOLLOW UP DAY 30	07-Nov-16	+33	71.7	38.1	1.88
CD66-01002	VISIT 5 FOLLOW UP DAY 100	18-Jan-17	+105	75.7	48.3	1.57

Samples for D7 and D14 were not sent to central laboratory
Response = PD

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01003	SCREENING PACK	24-Nov-16		17.6	189.6	0.09
CD66-01003	VISIT 2 PACK ^{90}Y TREATMENT	14-Dec-16	0	20.9	217.8	0.1
CD66-01003	VISIT 2 EXTENSION DAILY PACK	21-Dec-16	7	16.7	210.9	0.08
CD66-01003	VISIT 2 EXTENSION DAILY PACK	28-Dec-16	14	14.6	166.2	0.09
CD66-01003	VISIT 4 FOLLOW UP DAY 30	31-Jan-17	+34	15.4	181.1	0.09
CD66-01003	VISIT 5 FOLLOW UP DAY 100	18-Apr-17	+111	22	214.9	0.1

Response = stable disease

Cohort 2

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-02004	SCREENING PACK	28-Nov-2017	-	18.0	54.3	0.33
CD66-02004	VISIT 2 PACK ^{90}Y TREATMENT	13-Dec-2017	0	17.1	42.4	0.4
CD66-02004	VISIT 2 EXTENSION DAILY PACK	21-Dec-2017	8	13.7	26.0	0.53
CD66-02004	VISIT 3 EXTENSION POST TRANSPLANT	02-Jan-2017	20	13.8	32.2	0.43
CD66-02004	VISIT 4 FOLLOW UP DAY 30	31-Jan-2018	+35	19.4	33.7	0.58
CD66-02004	VISIT 5 FOLLOW UP DAY 100	11-Apr-2018	+107	14.3	34.5	0.41

Response = PR

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-03005	SCREENING PACK	19-Jul-2018	-	13.5	108.3	0.12
CD66-03005	VISIT 2 PACK ^{90}Y TREATMENT	19-Sept-2018	0	14.0	107.6	0.13
CD66-03005	VISIT 3 EXTENSION POST TRANSPLANT	26-Sept-2018	7	15.2	97.3	0.16
CD66-03005	VISIT 3 EXTENSION POST TRANSPLANT	03-Oct-2018	14	17.7	105.3	0.17
CD66-03005	VISIT 4 FOLLOW UP DAY 30	01-Nov-2018	+30	15.2	97.3	0.19
CD66-03005	VISIT 5 FOLLOW UP DAY 100	22-Jan-2019	+100	18.8	93.5	0.2

Response = PR

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01007	SCREENING PACK	23-Jan-2019	-	15.1	38.2	0.4
CD66-01007	VISIT 2 PACK ^{90}Y TREATMENT	12-Feb-2019	0	12.3	43.7	0.28
CD66-01007	VISIT 2 EXTENSION DAILY PACK	19-Feb-2019	7	13.1	42.3	0.31
CD66-01007	VISIT 2 EXTENSION DAILY PACK	26-Feb-2019	14	13.9	43.5	0.32
CD66-01007	VISIT 4 FOLLOW UP DAY 30	27-Mar-2019	+30	15.8	43.3	0.36
CD66-01007	VISIT 5 FOLLOW UP DAY 100	19-Jun-2019	+100	12.8	31.0	0.41

Response = PR

Patient CD66-01006 not recorded as they failed dosimetry and did not proceed to transplant.

Cohort 3

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01008	SCREENING PACK	11-Jun-19	-	12.2	694.9	0.02
CD66-01008	VISIT 2 PACK ^{90}Y TREATMENT	17-Jul-19	0	12.4	802.1	0.02
CD66-01008	VISIT 2 EXTENSION DAILY PACK	26-Jul-19	9	9.4	753.0	0.01
CD66-01008	VISIT 2 EXTENSION DAILY PACK	31-Jul-19	14	8.3	492.7	0.02
CD66-01008	VISIT 4 FOLLOW UP DAY 30	03-Sept-19	+34	9.4	466.5	0.02
CD66-01008	VISIT 5 FOLLOW UP DAY 100	05-Nov-19	+97	8.5	436.3	0.02

Response = PR

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01009	SCREENING PACK	15-Oct-19	-	21.4	37.7	0.57
CD66-01009	VISIT 2 PACK ^{90}Y TREATMENT	13-Nov-19	0	23.4	39.9	0.59
CD66-01009	VISIT 2 EXTENSION DAILY PACK	20-Nov-19	7	19.7	42.1	0.48
CD66-01009	VISIT 2 EXTENSION DAILY PACK	27-Nov-19	14	19.7	43.2	0.46
CD66-01009	VISIT 4 FOLLOW UP DAY 30	24-Dec-19	+27	23.2	32.6	0.71
CD66-01009	VISIT 5 FOLLOW UP DAY 100	07-Jul-20	+222	21.4	23.2	0.92

Response = CR

Patient ID	Visit Name	Date of Visit	Day Post Treatment/ transplant	Kappa (mg/L)	Lambda (mg/L)	Ratio
CD66-01010	SCREENING PACK	04-Feb-20	-	8.1	47.7	0.17
CD66-01010	VISIT 2 PACK ^{90}Y TREATMENT	04-Mar-20	0	5.4	109.7	0.05
CD66-01010	VISIT 2 EXTENSION DAILY PACK	11-Mar-20	7	6.7	66.7	0.10
CD66-01010	VISIT 2 EXTENSION DAILY PACK	18-Mar-20	14	6.0	54.3	0.11
CD66-01010	VISIT 4 FOLLOW UP DAY 30	27-Apr-20	+34	8.0	83.2	0.10
CD66-01010	VISIT 5 FOLLOW UP DAY 100	23-Jun-20	+127	7.7	56.2	0.14

Response = PR

Total FLC data timepoints points = 54
Actual data collected as per protocol (central laboratory) = 52
Data overall 96.3% complete.

Responses: CR 2; PR 5; Stable disease 1; Progressive disease 1.

Summary: Responses were demonstrated in 7/9 patients with 2 complete responses (CR) and 5 partial responses. One patient had stable disease and one patient showed a transient response before disease progression at D+100. Of note two patients showed further, slow falls in clonal FLC beyond D+100 one achieving CR.

2. To determine clonal response to the ^{90}Y-anti-CD66 mAb by following the change in malignant plasma cell population in bone marrow using an established, validated method of FLOW cytometry with a single central laboratory (Leeds HMDS).

Measure: Clonal plasma cell population determined by FLOW cytometry pre and post transplantation.

Table 4: Percentage of clonal plasma cells in BM pre and post-transplant

Patient ID	Plasma cell % pre-treatment		Plasma cell % D+100 post-transplant		Change
		Date of sample		Date of sample	
CD66-01001	1.42	08-Jul-2016	0.45	26-Nov-2016	- 69.4%
CD66-01002	0.7	24-Aug-2016	0.47	18-Jan-2017	- 32.9%
CD66-01003	0.12	24-Nov-2016	0.9	18-Apr-2017	+ 87%
CD66-02004	NA	28-Nov-2017	NA	09-May-2018	NA
CD66-03005	0.25	19-Jul-2018	0.303	22-Jan-2019	+ 82.5%
CD66-01007	0.334	23-Jan-2019	0.305	19-Jun-2019	- 9.3%
CD66-01008	3.2	11-Jun-2019	0.84	05-Nov-2019	- 74%
CD66-01009	0.72	15-Oct-2019	0.25	07-Jul-2020*	- 65%
CD66-01010	0.15	04-Feb-2020	0.05	23-Jun-2020*	- 67%

Total MRD data timepoints required = 18
Actual MRD data = 16.
Data overall 88.9% complete.

Summary: One patient had bone marrow samples sent to local laboratory not the central laboratory and these results were not recorded or analysed. Responses to the radiolabelled anti-CD66 as demonstrated by a fall in measurable disease was seen in 6/8 patients. Two patients showed an increase in the percentage of malignant plasma cells post therapy.

3. To determine disease response and cardiac recovery by measuring NT-proBNP levels pre and post (D100) therapy (centralised laboratory, NAC).

Measure: NT-proBNP levels pre and post (D100) therapy (pmol/L).

Table 5: NT-proBNP results pre and post-transplant

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01001	SCREENING PACK	08-Jul-2016	-	17.03
CD66-01001	VISIT 5 FOLLOW UP DAY 100	28-Nov-2016	+103	28.50

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01002	SCREENING PACK	24-Aug-2016	-	16.00
CD66-01002	VISIT 5 FOLLOW UP DAY 100	18-Jan-2017	+105	39.85

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01003	SCREENING PACK	24-Nov-2016	-	262.15
CD66-01003	VISIT 5 FOLLOW UP DAY 100	18-Apr-2018	+111	193.33

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-02004	SCREENING PACK	28-Nov-2017	-	28.40
CD66-02004	VISIT 5 FOLLOW UP DAY 100	09-May-2018	+107	14.66

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-03005	SCREENING PACK	19-Jul-2018	-	7.69
CD66-03005	VISIT 5 FOLLOW UP DAY 100	22-Jan-2019	+100	2.03

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01007	SCREENING PACK	23-Jan-2019	-	48.95
CD66-01007	VISIT 5 FOLLOW UP DAY 100	19-Jul-2019	+100	53.45

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01008	SCREENING PACK	11-Jun-2019	-	10.15
CD66-01008	VISIT 5 FOLLOW UP DAY 100	05-Nov-2019	+97	16.08

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01009	SCREENING PACK	15-Oct-2019	-	27.9
CD66-01009	VISIT 5 FOLLOW UP DAY 100	07-Jul-2020	+222*	34.65

Patient ID	Visit Name	Date of Visit	Day Post transplant	NT-proBNP
CD66-01010	SCREENING PACK	04-Feb-2020	-	229.5
CD66-01010	VISIT 5 FOLLOW UP DAY 100	23-Jun-2020	+127*	173.23

*Delayed timepoint due to COVID-19 restrictions.

Total expected data timepoints = 18.
Actual timepoints = 18.
Data overall 100% complete.

Summary:
No patients experienced a deterioration in cardiac function during the period of the study. There were no consistent changes in the level of NT-proBNP, in 5 patients there was an increase while in the remaining 4 patients there was a fall. Importantly the use of the radiolabelled antibody did not consistently result in a clinically relevant rise of the NT-proBNP as a marker of cardiac function.

4. To assess impact of using [^{90}Y]-labelled anti-CD66 mAb on time to progression and overall survival.

Measure: Assessment of Time to disease Progression (TTP) and Overall Survival (OS).

Time to disease progression:

During the period of follow-up within the study one patient, CD6601-002, showed evidence of disease progression with rising FLCa at Day+100 post-transplant. One patient, CD6601-003, after an initial response as determined by a fall in clonal FLCa had an increase in FLCa to same level as measured in the screening visit and therefore was classified as 'stable disease'.

Overall Survival:

No patients died within the trial follow-up period of Day +100 post-transplant. All patients remain alive at the time of data verification and lock (25-Jun-2021), OS 100% with median survival of 32.81 months (mean 36.57 months); range 15.32 – 58.36 months.

5. To determine the utility of the dosimetry model developed in previous Phase I and II trials, using the same radiolabelled anti-CD66 and with imaging/dosimetry post ^{90}Y-labelled anti-CD66.

Measure: Comparison of organ dosimetry from previous trials using the same antibody vector.

See details of organ dosimetry in table 6.

Summary: The biodistribution of the ^{111}In-anti-CD66 in patients with S-ALA was the same as seen in previous studies. The dosimetry model used in previous trials using the same IMP was of the same utility as in previous trials with highest levels of activity detected in the red marrow and spleen. One patient, CD66-01006, had higher uptake in the liver than permitted in the study protocol and did not proceed to transplant. It was unclear why the hepatic uptake was unusually high in this subject.

Table 2: Organ dosimetry

		Estimated Organ Radiation Dose in Gray (Gy)					
Patient ID	Infused activity ^{90}Y MBq	BM	Liver	Spleen	Lung	Renal	Whole body
Cohort 1							
CD66-01001	1158	24.1	6.3	38.6	1.4	13.6	0.7
CD66-01002	2262	41.1	8.0	10.9	1.6	2.7	0.7
CD66-01003	2013	39.0	3.9	31.4	1.3	3.4	0.8
Cohort 2							
CD66-02004	2985	44.5	4.5	13.5	1.6	2.5	1.0
CD66-03005	1867	45.0*	5.4	22.0	1.0	1.6	1.2
CD66-01006**	2680	19.4	24.2	13.7	3.6	1.7	0.9
CD66-01007	2323	31.2	8.5	19.0	2.6	2.6	1.2
Cohort 3							
CD66-01008	1734	31.6	15.0#	41.4	1.1	2.6	1.1
CD66-01009	2019	37.6	5.9	13.7	2.0	3.4	1.0
CD66-01010	2570	45.0*	9.2	53.1	1.9	2.2	1.1

*Infused activity of ^{90}Y-anti-CD66 reduced to limit BM radiation dose to 45Gy

**Based on ^{111}In-anti-CD66 gamma imaging and dosimetry patient CD66-01006 exceeded estimated hepatic radiation dose and the BM:liver ratio was not 2:1; patient did not receive therapy.

#Liver dose capped at 15Gy – infused activity reduced to 42.2MBq/kg lean body weight

Data completeness 100%

6. To determine the engraftment of autologous stem cells as determined by time to platelet recovery > 20 and >50 x 10^9/L and neutrophils >0.5 x 10^9/L (EBMT criteria). Engraftment greater than 28 days post transplantation would be outside that anticipated for patients receiving autologous stem cell transplantation using standard conditioning protocols.

Note: The results for platelets >50 x 10^9/L is complicated by early discharge of patients once a stable, unsupported platelet count has been achieved.

Measure: Tabulation of platelet and neutrophil engraftment.

Table 6: Engraftment

Cohort 1

Patient ID	Visit Name	Neutrophils >0.5	Plt > 20	Plt >50
CD66-01001	VISIT 3 EXTENSION POST TRANSPLANT	+15	+12	+15
CD66-01002	VISIT 3 EXTENSION POST TRANSPLANT	+14	+10	+17
CD66-01003	VISIT 3 EXTENSION POST TRANSPLANT	+25	+11	+34
Mean Days		**18**	**11**	**22**
Median Days		**15**	**11**	**17**

Cohort 2

Patient ID	Visit Name	Neutrophils >0.5	Plt > 20	Plt >50
CD66-02004	VISIT 3 EXTENSION POST TRANSPLANT	+10	+11	+42
CD66-03005	VISIT 3 EXTENSION POST TRANSPLANT	+13	Never <20	+13
CD66-01007	VISIT 3 EXTENSION POST TRANSPLANT	+11	+10	+29
Mean Days		**11.3**	**10.5**	**28**
Median Days		**11**	**10.5**	**29**

Cohort 3

Patient ID	Visit Name	Neutrophils >0.5	Plt > 20	Plt >50
CD66-01008	VISIT 3 EXTENSION POST TRANSPLANT	+13	+9	+12
CD66-01009	VISIT 3 EXTENSION POST TRANSPLANT	+13	+11	+14
CD66-01010	VISIT 3 EXTENSION POST TRANSPLANT	+12	+11	+40
Mean Days		**12.7**	**10.3**	**22**
Median Days		**13**	**11**	**14**

Overall results:
Time to neutrophil engraftment: Mean = 14; median = 13
Time to plt > 20 engraftment: Mean = 10.6; median = 11
Time to plt >50 engraftment: Mean = 24; median = 17

Summary:

All patients experienced grade 3 – 4 cytopenia indicating that even at the lowest infused activity of Y-90 labelled anti-CD66 significant BM suppression was induced by the targeted radiation.

All patients engrafted neutrophils and platelets within time periods very similar to those expected for standard autologous stem cell transplant engraftment times. The result for platelet recovery >50 in patient CD66-01010 was longer than the mean due to early discharge of the patient and the first follow-up post discharge was D+40.

Data return 100%.

7. To assess the proportion of patients that form human anti-murine antibodies (HAMA) following exposure to anti-CD66 mAb in the context of an autologous stem cell transplant for AL amyloidosis.

Measure: HAMA assay results from samples taken at defined intervals post transplantation.

Table 7: HAMA post-transplant

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01001	SCREENING PACK	08-Jul-2016	Screening	Negative
CD66-01001	VISIT 5 FOLLOW UP DAY 100	28-Nov-2016	+103	Positive

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01002	SCREENING PACK	24-Aug-2016	Screening	Negative
CD66-01002	VISIT 5 FOLLOW UP DAY 100	18-Jan-2017	+105	Positive

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01003	SCREENING PACK	24-Nov-2016	Screening	Negative
CD66-01003	VISIT 5 FOLLOW UP DAY 100	18-Apr-2018	+111	Negative

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-02004	SCREENING PACK	28-Nov-2017	Screening	Negative
CD66-02004	VISIT 5 FOLLOW UP DAY 100	09-May-2018	+107	Positive

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-03005	SCREENING PACK	19-Jul-2018	Screening	Negative
CD66-03005	VISIT 5 FOLLOW UP DAY 100	22-Jan-2019	+100	Positive

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01007	SCREENING PACK	23-Jan-2019	Screening	Negative
CD66-01007	VISIT 5 FOLLOW UP DAY 100	19-Jul-2019	+100	Negative

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01008	SCREENING PACK	11-Jun-2019	Screening	Negative
CD66-01008	VISIT 5 FOLLOW UP DAY 100	05-Nov-2019	+97	Negative

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01009	SCREENING PACK	15-Oct-2019	Screening	Negative
CD66-01009	VISIT 5 FOLLOW UP DAY 100	07-Jul-2020	+222*	Positive

Patient ID	Visit Name	Date of Visit	Day Post transplant	HAMA result
CD66-01010	SCREENING PACK	04-Feb-2020	Screening	Negative
CD66-01010	VISIT 5 FOLLOW UP DAY 100	23-Jun-2020	+127*	Positive

Summary:

All patients had to be negative for HAMA as a criterion for trial entry. Post exposure to the radiolabeled anti-CD66 six (6) of nine (9) patients became serologically positive for human anti-murine antibodies. There is no clinical significance of forming HAMA.

Data returns: 100%

Conclusions

The study achieved the primary end-point and all of the secondary end-points. The IMP preferentially localised to the bone marrow in all except one patient, of the 9 patients that passed dosimetry, disease responses were seen in 7 patients with two achieving CR by Day+100 post-transplant. These data, including AEs, of each treatment cohort were reviewed by the IDMC and no concerns were raised.

Primary End-point: This was achieved with evidence of minimal toxicity from the ^{90}Y-anti-CD66 targeted radiotherapy. There were no infusion related AEs, consistent with previous experience with the IMP. Post treatment all patients became profoundly cytopenic but had none of the toxicities associated with standard transplant conditioning. Importantly, all patients maintained oral nutrition and no therapy related diarrhoea. Two patients experienced fevers, one due to a urinary tract infection, the other with no identified source, neither were life-threatening. No dose limiting toxicity was seen.

Secondary end-points:

1) Disease responses as determined by changes in clonal FLCa. Disease responses using this criterion were demonstrated with 2 patients achieving a CR by Day+100 post-transplant, 5 patients achieved PRs. Considering the lack of toxicity this was an important finding. Two patients showed continued decrease in clonal FLCa beyond Day+100.

2) Disease responses as determined by changes in the percentage of clonal plasma cells (cPC%) in bone marrow. Of the nine patients that received therapy and ASCT 8 were evaluable. Of these 6 showed a decrease in the cPC%.

Taken together the two indicators of disease response demonstrated a definite disease reduction in the majority of patients.

3) Cardiac recovery using NT-proBNP. There were no consistent changes in the level of NT-proBNP in the study. Two patients had an increase of NT-proBNP, three a reduction and in four patients a change of <10%. Importantly no patients experienced cardiac toxicities during the study. Longer follow-up may be required to determine if patients with significantly elevated NT-proBNP have any improvement.

4) An important parameter of a new therapy is the interval until disease progression. This study had a short follow-up period, mainly because the primary aim was to determine the toxicity of treatment rather than disease response and duration of response. Of the none patients that were treated and underwent ASCT only one had evidence of disease progression with a rise in FLCa at Day+100. Further follow-up beyond Day+100 will provide additional evidence of the durability of responses. In addition, the time to next treatment is also an important measure of the effectiveness of a new therapy.

Overall survival in the study was 100% at Day+100 and remains 100% with median follow-up of 32.8 months (range 15.3 – 58.4 months). This is excellent for patients with S-ALA undergoing ASCT. However the number of patients in this study was small and was not designed or powered to test whether TTP and OS were better than with standard ASCT conditioning.

5) The biodistribution and dosimetry derived from sequential gamma images was consistent with the results from previous trials using the same IMP. One patient had high hepatic uptake of the ^{111}In-anti-CD66, this has been seen in other studies but usually a cause has been identified. In this patient no specific cause was identified.

The estimated absorbed radiation dose to the bone marrow varied between patients with no correlation between infused activity and BM radiation dose unlike previous studies. This may be due to the small size of each cohort, the previous Phase I trial had 5 patients per infused activity cohort. There was good consistency when the dosimetry was expressed as centiGray absorbed radiation divided by infused activity in MBq (cGy/MBq) which should be similar irrespective of the actual infused activity. Table 3 shows the relationship between infused activity, estimated absorbed organ radiation dose and radiation dose expressed as cGy/MBq. The median to bone marrow was 18.2 and the mean 17.24 cGy/MBq (18.35 and 18.22 respectively excluding patient CD6601006) range 7.24 – 20.81. This is slightly higher than previously seen in the larger Phase I trial in a wide range of haematological malignancies where the median was 14.01, mean 14.68 cGy/MBq although the ranges are similar 10.81 – 22.26 cGy/MBq. Again this may in part be due to the smaller size of the patient group in the TRALA study (n=10). These data confirm the similar biodistribution in patients with S-ALA and the dosimetry model was applicable.

6) All patients engrafted within the timeframe expected for patients receiving autologous stem cell transplants and there were no primary or secondary graft failures.

Recommendations for future research:

The lack of toxicity, particularly the complete absence of mucositis, but with disease responses would indicate that the ^{90}Y-anti-CD66 could offer an effective treatment option for patients with S-ALA. Several new agents effective in myeloma have shown considerable activity in S-ALA including monoclonal antibodies such as Daratuzumab. Although able to induce excellent responses the majority of patients will relapse. While ASCT remains an option for S-ALA the use of targeted radiotherapy could have an important role in providing a method of consolidation or for treatment of relapsed/refractory disease with minimal toxicity. Future trials could explore the use of a standard dose of radiation to the bone marrow. In addition, DNA-damage repair inhibitors could be used to augment the beneficial effect of targeted radiation.

Appendix 1 Patient characteristics

Study ID	Age Yrs	M/F	S-ALA clone	Amyloid deposition	Previous number of treatments	Comorbidities	NYHA cardiac grade
Cohort 1							
CD6601-001	68	F	Lambda	Renal, spleen	4	Nephrotic syndrome, CKD 1	1
CD6601-002	55	M	Kappa	Hepatic, renal. spleen	2	Nephrotic syndrome, CKD 1	1
CD6601-003	69	M	lambda	Renal, spleen, cardiac	2	Nephrotic syndrome, CKD 1, cardiac arrhythmias, indwelling defibrillator	2
Cohort 2							
CD6602-004	56	M	Lambda	Renal	1	Nephrotic syndrome, CKD 1	1
CD6603-005	58	M	Lambda	Gut	2	Previous GI haemorrhage	1
CD6601-007	67	M	Lambda	Cardiac, tongue	3*	CKD 1	1
Cohort 3							
CD6601-008	70	F	Lambda	Renal	4*	Nephrotic syndrome, CKD 3	0
CD6601-009	62	F	Lambda	Cardiac, renal	1	Nephrotic syndrome, CKD 2	0
CD6601-010	69	M	Lambda	Cardiac, renal	3*	Nephrotic syndrome, CKD 2	0

*Patients had received previous autologous SCT with HD melphalan

CKD – Chronic kidney disease, grades 1 -

Appendix 2: Full list of Adverse Events

Patient ID	Visit widow	Adverse Event	Start Date	Resolution Date	Severity	Action taken with Study Medication	Outcome	Relationship	Serious	Result in Withdrawal
CD66-01001	POST ^{90}Y AND STEM CELL FOLLOW UP	NAUSEA	05-Aug-16	12-Aug-16	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01001	POST ^{90}Y AND STEM CELL FOLLOW UP	SORE THROAT	17-Aug-16	18-Aug-16	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01001	POST ^{90}Y AND STEM CELL FOLLOW UP	PRE-SYNCOPE	17-Aug-16	18-Aug-16	2 = MODERATE	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01001	POST ^{90}Y AND STEMCELL FOLLOW UP	PAIN (HIP)	17-Aug-16	19-Aug-16	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01001	POST ^{90}Y AND STEM CELL FOLLOW UP	CONSTIPATION	22-Aug-16	29-Aug-16	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01002	POST ^{90}Y AND STEM CELL FOLLOW UP	MILD HEADACHE	28-Sep-16	28-Sep-16	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01002	POST ^{90}Y AND STEM CELL FOLLOW UP	HEADACHE	06-Oct-16	07-Oct-16	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01003	POST ^{90}Y AND STEM CELL FOLLOW UP	MILD NAUSEA	29-Dec-16	07-Jan-17	1 = MILD	NOT APPLICABLE	RESOLVED	UNRELATED	NO	NO
CD66-01003	POST ^{90}Y AND STEM CELL FOLLOW UP	DIZZINESS (SYNCOPE)	19-Jan-17	31-Jan-17	1 = MILD	NOT APPLICABLE	RESOLVED	UNRELATED	NO	NO

Patient ID	Visit widow	Adverse Event	Start Date	Resolution Date	Severity	Action taken with Study Medication	Outcome	Relationship	Serious	Result in Withdrawal
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Diarrhoea (Norovirus)	18-Dec-2017	28-Feb-2017	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Oedema (feet)	19-Dec-2017	28-Dec-2017	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Epigastric pain	25-Dec-2017	UNK	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Neutropenia (febrile)	27-Dec-2017	09-Jan-2018	3 = SEVERE	NONE	RESOLVED	UNRELATED	YES	NO
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Cough	01-Jan-2018	09-Jan-2018	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Fatigue	17-Jan-2018	28-Feb-2018	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-02004	POST ^{90}Y AND STEM CELL FOLLOW UP	Minor leg oedema	31-Jan-2018	20-May-2018	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO

Patient ID	Visit widow	Adverse Event	Start Date	Resolution Date	Severity	Action taken with Study Medication	Outcome	Relationship	Serious	Result in Withdrawal
CD66-03005	DOSIMETRY +90Y TREATMENT	Pain and Extremity	17-Sep-2018	18-Sept-2019	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-03005	POST ^{90}Y AND STEM CELL FOLLOW UP	Jejunal haemorrhage	10-Oct-2018	16-Oct-2018	3 = SEVERE	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-03005	POST ^{90}Y AND STEM CELL FOLLOW UP	Flu-like symptoms	16-Oct-2018	18-Oct-2018	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-03005	POST ^{90}Y AND STEM CELL FOLLOW UP	Urinary frequency	16-Oct-2018	18-Oct-2018	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-03005	POST ^{90}Y AND STEM CELL FOLLOW UP	Sore throat	16-Oct-2018	18-Oct-2018	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01006	POST In-111	NONE	-	-	-	-	-	-	-	-
CD66-01007	POST ^{90}Y AND STEM CELL FOLLOW UP	Oral candidiasis	27-Feb-2019	06-Mar-2019	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01007	POST ^{90}Y AND STEM CELL FOLLOW UP	Dizzy	03-Mar-2019	05-Mar-2019	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01007	POST ^{90}Y AND STEM CELL FOLLOW UP	Dehydrated	03-Mar-2019	05-mAR-2019	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01007	POST ^{90}Y AND STEM CELL FOLLOW UP	Breathlessness (dyspnoea)	09-Mar-2019	10-Mar-2019	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO

Patient ID	Visit widow	Adverse Event	Start Date	Resolution Date	Severity	Action taken with Study Medication	Outcome	Relationship	Serious	Result in Withdrawal
CD66-01008	POST ^{90}Y AND STEM CELL FOLLOW UP	BACK PAIN	08-Jul-19	17-Jul-19	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01008	POST ^{90}Y AND STEM CELL FOLLOW UP	POSITIVE URINALYSIS	08-Jul-19	24-Jul-19	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01008	POST ^{90}Y AND STEM CELL FOLLOW UP	FALL	12-Jul-19	12-Jul-19	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01008	POST ^{90}Y AND STEM CELL FOLLOW UP	LOWER BACK PAIN	21-Jul-19	26-Jul-19	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01008	POST ^{90}Y AND STEM CELL FOLLOW UP	UTI	08-Aug-19	12-Aug-19	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01008	POST ^{90}Y AND STEM CELL FOLLOW UP	E.coli in urine	16-Aug-19	23-Aug-19	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	LOWER RESPIRATORY TRACT INFECTn	-	-	1 = MILD	NONE	RESOLVED	UNLIKELY	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	EPISTAXIS (nose bleed)	01-Dec-19	10-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	UTI	03-Dec-19	09-Dec-19	2 = MODERATE	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	BRUISING	03-Dec-19	-	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	CONSTIPATION	04-Dec-19	09-Dec-19	2 = MODERATE	NONE	RESOLVED	UNRELATED	NO	NO

CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	LIGHT-HEADEDNESS	05-Dec-19	07-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	NEUTROPENIC FEVER	06-Dec-19	06-Dec-19	4 = SEVERE	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	CHEST PAIN	06-Dec-19	07-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	HEART MURMUR	06-Dec-19	08-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	PALPITATIONS	06-Dec-19	08-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	ANAL PAIN	06-Dec-19	11-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	ABDO PAIN	06-Dec-19	11-Dec-19	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	SOB	13-Dec-19	20-Jan-20	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01009	POST ^{90}Y AND STEM CELL FOLLOW UP	PALPITATIONS	13-Dec-19	20-Jan-20	1 = MILD	NONE	RESOLVED	UNRELATED	NO	NO
CD66-01010	POST ^{90}Y AND STEM CELL FOLLOW UP	DIZZINESS (SYNCOPE)	24-Feb-20	24-Feb-20	1 = MILD	NOT APPLICABLE	RESOLVED	UNRELATED	NO	NO
CD66-01010	POST ^{90}Y AND STEM CELL FOLLOW UP	HYPOTENSION	31-Mar-20	31-Mar-20	1 = MILD	NOT APPLICABLE	RESOLVED	UNRELATED	NO	NO

Cumulative total of 47 AEs and no SAEs. Mild (CTCAE grade 1) = 41; Moderate (CTCAE grade 2) = 3; Severe (CTCAE grade 3,4) = 3

Appendix 3 Estimated absorbed radiation dose for the bone marrow and liver as cGy/MBq

Patient ID	Infused activity ^{90}Y MBq	BM Gy	BM cGy/MBq	Liver Gy	Liver cGy/MBq
CD66-01001	1158	24.1	20.81	6.3	5.44
CD66-01002	2262	41.1	18.17	8.0	3.54
CD66-01003	2013	39.0	19.37	3.9	1.94
CD66-02004	2985	44.5	14.91	4.5	1.51
CD66-03005	1867	45.0*	24.10	5.4	2.89
CD66-01006**	2680	19.4	7.24	24.2	9.03
CD66-01007	2323	31.2	13.43	8.5	3.66
CD66-01008	1734	31.6	18.22	15.0#	8.65
CD66-01009	2019	37.6	18.62	5.9	2.92
CD66-01010	2570	45.0*	17.51	9.2	3.58
Median	-	-	**18.20**	-	**3.56**
Mean	-	-	**17.24**	-	**4.32**

*Infused activity of ^{90}Y-anti-CD66 capped at the limit of estimated BM radiation dose at 45Gy
**Patient did not receive ^{90}Y-anti-CD66 due to adverse dosimetry
Infused activity of ^{90}Y-anti-CD66 capped at the limit of estimated radiation dose to liver of 15Gy

Range for BM 7.25 – 20.81 cGy/MBq (13.34 – 20.81 if patient CD6601-006 excluded); for liver range 3.90 – 15.00 (3.9 – 8.65 if patient CD6601-006 excluded).

Previous results from 55 patients in earlier Phase I trial in a range of haematological malignancies: median and mean 14.01 and 14.68 cGy/MBq for BM and for liver 2.56 and 2.61 cGy/MBq respectively. Range for BM 6.52 – 22.26 cGy/MBq and for liver 0.56 – 5.58 cGy/MBq.

Trial registration
This trial was registered as ISRCTN13400668

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